



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶: A61K 31/40	A1	(11) International Publication Number: WO 96/39136 (43) International Publication Date: 12 December 1996 (12.12.96)
(21) International Application Number: PCT/EP96/02435 (22) International Filing Date: 4 June 1996 (04.06.96) (30) Priority Data: 9511366.8 6 June 1995 (06.06.95) GB (71) Applicant (for all designated States except US): SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB). (72) Inventor; and (75) Inventor/Applicant (for US only): PATEL, Anil [GB/BE]; SmithKline Beecham Pharmaceuticals, Mundells, Welwyn Garden City, Hertfordshire AL7 1EY (GB). (74) Agent: CONNELL, Anthony, Christopher; SmithKline Beecham, Corporate Intellectual Property, SB House, Great West Road, Brentford, Middlesex TW8 9BD (GB).		(81) Designated States: JP, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: TRANSDERMAL FORMULATION COMPRISING ROPINIROLE (57) Abstract Transdermal formulations comprising ropinirole for use in treating Parkinson's Disease.		

FOR THE PURPOSES OF INFORMATION ONLY

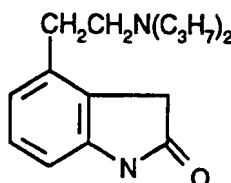
Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

TRANSDERMAL FORMULATION COMPRISING ROPINIROLE

The present invention relates to a transdermal formulation comprising 4-(2-di-*n*-proylaminoethyl)-2(3H)-indolone and for the use thereof in treating Parkinson's
5 Disease.

4-(2-di-*n*-proylaminoethyl)-2(3H)-indolone (hereinafter referred to by its approved name Ropinirole) is the compound of formula (I):



(I)

This compound was first disclosed in EP 0 113 964-A1 (SmithKline Beckman Corp) as a peripheral, pre-synaptic D₂-agonist, suitable for use in treating angina and
15 hypertension. Subsequently, it was also shown to have central effects, as a post-synaptic D₂-agonist in the brain (EP 0 299 602-A2, Smith Kline & French Laboratories). Furthermore, tolerance was developed to the peripheral effects. These central effects have led to the compound (as the hydrochloride salt) being developed for use in treating Parkinson's Disease, by oral administration of a tablet formulation.

20 EP 0 299 602-A2 further discloses that other forms of administration may be considered for ropinirole and salts thereof, including parenteral, rectal and transdermal. A typical transdermal formulation is said to comprise a conventional aqueous or non-aqueous vehicle, for example, a cream, ointment lotion or paste in the
25 form of a medicated plaster, patch or membrane. There is however no further guidance on suitable transdermal formulations or expected dosage for such formulations.

A transdermal formulation offers the advantage of a more convenient mode of
30 administration of the drug substance, thereby potentially enhancing patient compliance. In addition, drug substance is released in a more controlled fashion, over a prolonged period, offering potential therapeutic advantages.

It has now been found that improved transdermal formulations able to provide a
35 therapeutically useful amount of the drug may be prepared by using the free base

form of the compound, in comparison to the hydrochloride salt preferred for tablet formulation.

Accordingly, the present invention provides for a transdermal formulation comprising
5 ropinirole (free base).

Such formulations offer not only a more convenient method of administration but also possible therapeutic benefits and improved side effect profile.

- 10 Suitable transdermal formulations are well known in the art (see for instance Percutaneous Absorption and Transdermal Therapy, K A Walters, March 1986; Pharmaceutical Dosage Forms and Drug Delivery Systems, (5th Ed.), H C. Ansel and N G. Popovich, Chapter 9, Lea and Febiger (1990), pages 307 to 320 and Sustained and Controlled Release Drug Delivery Systems, ed J R Robinson, Marcel Dekker
15 Inc., New York (1978), pages 579 *et seq.*). Two main types of transdermal delivery devices are currently marketed and these are classified as matrix and membrane systems (Physicochemical Principles of Pharmacy, A.T. Florence and D. Attwood, 2nd Edition, Macmillan, 1993, page 331). In matrix systems, the drug is dispersed in a release controlling matrix which consists either of a gel or an adhesive film.
20 Membrane systems generally consist of a drug reservoir, a rate-controlling membrane and an adhesive layer. In both cases the active is dissolved or suspended in a vehicle which then forms an integral part of the delivery device. The drug substance may be dissolved or suspended in a liquid or a gel. Suitable vehicles include both aqueous and non-aqueous vehicles, for instance saline and saline/propylene glycol (1:1). A
25 penetration enhancer may also be added, if appropriate.

Suitably, the transdermal formulation is provided in the form of a medicated plaster, patch or membrane, preferably a patch. Suitably the patch is between 10 and 50cm², preferably between 20 and 40 cm². The patch will be provided with a
30 pharmaceutically acceptable adhesive layer so that it can be retained on the skin of the user. Preferably the adhesive effect of the layer will be reversible such that the patch will remain in place for the lifetime of the patch but still be easy for the Parkinson's Disease patient to apply and remove.

35 In a further aspect, ropinirole free base may be generated *in situ* in the transdermal formulation, from a suitable ropinirole salt such as ropinirole hydrochloride, suitably immediately prior to use. Suitably this may be achieved by including in the formulation a base which would be brought into contact with the ropinirole salt to effect formation of the free base. The salt and base are kept apart, to avoid premature reaction, for

instance in a two compartment reservoir having a rupturable barrier between the two compartments.

Suitably, a preliminary evaluation of transdermal candidates is performed prior to
5 incorporation in such a device. The most effective method is to determine drug penetration from suspensions or solutions using a human skin *in vitro* model, such as the Franz cell (Dermatological Formulations: Percutaneous Absorption, B W Barry, Marcel Dekker (1983), page 245).

10 Preferably, the delivery profile will provide a steady rate delivery. Alternatively, a compartmentalised rate controlled device may used. A suitable target skin flux will be in the range 5 to 25, preferably 10 to 15 $\mu\text{g}/\text{cm}^2/\text{hr}$.

Suitably, the amount of ropinirole administered through a transdermal formulation
15 according to the present invention will be selected so that it will provide an amount of ropinirole substantially similar to that obtained following conventional oral administration of a tablet formulation, that is substantially similar to that obtained following administration of between 0.1 and 10mg of ropinirole (expressed as the free base) three times a day, assuming about 50% bioavailability.

20 Suitably the transdermal formulation is provided in unit dose form. Suitably, the transdermal formulation is provided in a range of dosage amounts, for instance to allow for titration of an individual patient's drug requirement. A suitable dose may be obtained by combining different strength formulations. Suitably, the unit dose form
25 will provide sufficient drug substance for a 24 hour period (including, if appropriate 'off time'), to permit once-a-day application of the formulation. Suitably such application may be in the evening. Suitably, the transdermal formulation will be administered for a period of continuous therapy.

30 Transdermal formulations according to the present invention will be of use in therapy, in particular treating Parkinson's Disease. Accordingly, in a further aspect, the present invention provides for the manufacture of a medicament comprising ropinirole (free base) adapted for a transdermal administration for use in treating Parkinson's Disease. The transdermal formulation may be used in patients in all
35 stages of disease and/or as therapy after initial dose titration with a conventional tablet.

The invention will now be illustrated by the following examples.

Description 1 - preparation of ropinirole

Ropinirole hydrochloride (190gm), water (1.35L) and ammonia (160mL, SG 0.88) were added to a flask fitted with stirrer and nitrogen bleed. This mixture was then stirred at ambient for ca 2 hours and then extracted with dichloromethane (1x500mL, 1x 250mL, 1x 200mL). All the organic extracts were combined, washed with brine (3x50mL) and dried over with magnesium sulphate (if free water was still present). Removal of the solvent by evaporation under reduced pressure gave a light brown solid (142gm, 85% yield).

10

NMR [δ H(CDCl₃)]: 0.9(6H,t), 1.5(4H,m), 2.7(3H,s), 3.5(2H,s), 6.7-6.9(3H,m,Ar), 8.6(2H,br,NH).

Example 1

15

A typical patch comprising a membrane is as follows:

a backing layer of aluminized plastic that is impermeable to ropinirole;
drug reservoir containing ropinirole (30 to 60mg/ml) in a saline/propylene glycol (1:1) vehicle;
ethylene-vinyl acetate copolymer membrane that is permeable to ropinirole; and
a layer of hypoallergenic silicone adhesive;
plus a protective peel strip covering the adhesive surface.

patch size = 20-40cm²
reservoir volume = 0.5-1ml

Example 2

30 A typical patch comprising a matrix is as follows:

backing foil;
drug reservoir comprising a ropinirole/lactose trituration homogeneously dispersed in a hydrogel composed of water, glycerin, poly vinyl alcohol and polyvinylpyrrolidone;
adhesive layer; and
a release liner.

Example 3 - *in vitro* Percutaneous Penetration of Ropinirole

The relative potential of ropinirole (as the free base) and a ropinirole salt for formulation into a transdermal delivery system was initially evaluated by determining drug penetration from suspensions or solutions using a human skin *in vitro* model.

The *in vitro* percutaneous penetration method utilised saturated solutions of ropinirole hydrochloride and ropinirole free base. The *in vitro* set up consisted of modified Franz cells (Dermatological Formulations: Percutaneous Absorption. B.W. Barry, Marcel Dekker, 1983, 245) with full thickness human abdominal skin and a receptor of 0.9% saline. The vehicles tested were ropinirole and its hydrochloride salt in aqueous 0.9% saline and aqueous 0.9% saline/propylene glycol (50:50). Samples were taken from the receptor at intervals and analysed for ropinirole content. From these results the concentration of ropinirole penetrating human skin with time could be determined.

Results

Formulation	Penetration Over 24 hours $\mu\text{g}/\text{cm}^2$ (SEM) [Rel to 1]	Penetration over 96 hours $\mu\text{g}/\text{cm}^2$ (SEM) [Rel to 1]
Ropinirole Hydrochloride		
1. 0.9% Saline	0.86 (0.24) [1.0]	3.52 (0.50) [1.0]
2. 0.9% saline: PG (50:50)	0.23 (0.04) [0.27]	2.62 (0.40) [0.74]
Ropinirole Free Base		
3. 0.9% Saline	18.20 (4.84) [21.2]	29.66 (5.75) [8.4]
4. 0.9% Saline: PG (50:50)	10.45 (4.20) [12.2]	83.88 (10.87) [23.8]

(SEM) = Standard Error of Mean

[Rel to 1] = Skin penetration relative to formulation 1

PG = Propylene glycol

Conclusions

- Penetration of the free base appears to be 20 fold better than the salt from the
- 5 0.9% saline vehicle and 40 fold better from the PG: saline vehicle.

Using this test system, 10-20 μg of the free base penetrated through the skin over a 24 hour period. Thus, with a patch of 30 cm^2 , potentially 300-600 μg of drug could be delivered, to give therapeutically effective blood levels of ropinirole.

Claims

1. A transdermal formulation comprising ropinirole (free base).
- 5 2. A transdermal formulation as claimed in claim 1 which has a target skin flux of from 5 to 25 $\mu\text{g}/\text{cm}^2/\text{hr}$.
2. A transdermal formulation as claimed in claim 1 in the form of a patch.
- 10 3. A transdermal formulation as claimed in claim 1 or 2 in the form of a unit dosage, comprising between 1 and 20 mg of ropinirole.
4. A transdermal formulation as claimed in any one of claims 1 to 3 in which ropinirole free base is generated *in situ*.
- 15 5. A transdermal formulation as claimed in any one of claim 1 to 4 adapted for once-a-day application.
6. The manufacture of a medicament comprising ropinirole (free base) adapted for
20 transdermal administration for treating Parkinson's Disease.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 96/02435

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 299 602 (SMITH KLINE) 18 January 1989 cited in the application see abstract see page 3, line 6 - line 8 see page 3, line 39 - line 43; claims ---	1-6
A	THE NEW ENGLAND JOURNAL OF MEDICINE, vol. 329, no. 14, 1993, pages 1021-1027, XP002013778 D.B. CALNE: "TREATMENT OF PARKINSON'S DISEASE" see page 1026; table 3 --- -/--	1-6

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

19 September 1996

Date of mailing of the international search report

07.10.96

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Hoff, P

INTERNATIONAL SEARCH REPORT

Int'l Application No

PCT/EP 96/02435

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PHARMACEUTICAL DOSAGE FORMS AND DRUG DELIVERY SYSTEMS 5TH ED., CHAPTER 9, 1990, pages 307-320, XP002013779 H.C. ANSEL ET AL.: "TRANSDERMAL DRUG DELIVERY SYSTEMS, OINTMENTS, CREAMS, LOTIONS, AND OTHER PREPARATIONS" cited in the application see the whole document ---	1-6
A	"FORMES PHARMACEUTIQUES NOUVELLES" 1988 , LAVOISIER , PARIS XP002013798 VOIE PERCUTANEE see page 385 - page 409 -----	1-6

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 96/02435

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-299602	18-01-89	AU-B- 599792	26-07-90
		AU-A- 1644588	24-11-88
		CA-A- 1305421	21-07-92
		DE-A- 3876877	04-02-93
		DK-B- 169609	27-12-94
		ES-T- 2052717	16-07-94
		IE-B- 63511	03-05-95
		JP-C- 1879525	21-10-94
		JP-B- 6002672	12-01-94
		JP-A- 63303966	12-12-88
		US-A- 4824860	25-04-89
		US-A- 4912126	27-03-90
